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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/458,610	12/10/99	NABEL E	8642/88

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EXAMINER	
BECKERLEG,A	
ART UNIT	**PAPER NUMBER**
1632	11

DATE MAILED: 07/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/458,610	Applicant(s) NABEL ET AL.	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response to the restriction/election received on 5/2/01 has been entered. The applicants elected without traverse Group II, claims 31-32 and 69-104, in paper no. 9. However, it is noted that the applicant has canceled all previously pending claims, and added new claims 106-142 which correspond to the subject matter of elected Group II. Claims 106-142 are therefore pending and active in the instant application. An action on the merits follows.

The drawings are objected to because of minor informalities which are identified in detail by the attached PTO form 948. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 106-142 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. The specification discloses the treatment of disease by the site-specific installation of cells. The cells can be non-transfected primary cells, or cells transfected *in vitro* with a nucleic acid encoding a therapeutic gene. The specification further discloses the site-specific installation of transfected endothelial cells to blood vessels *in vivo* using a balloon catheter. It is noted that the specification does not provide guidance for the site-specific administration of cells *in vivo* for any use other than for the treatment of disease.

The specification does not provide an enabling disclosure for the site-specific installation of any and all cells to any and all sites in a mammal such that a therapeutic level of gene expression from said cells is observed and results in some detectable therapeutic effect on any disease symptom or condition. The specification reads on the installation of xenogeneic or allogeneic cells into a mammal. In the absence of substantial immunodeficiency, foreign tissue is rapidly rejected by the host mammal's immune system. Rejection is largely mediated by complement, cytotoxic T cells, and antibody-dependent cellular cytotoxicity. Antibody mediated rejection of tissue is particularly strong in the case of discordant xenogeneic tissue due to the presence of preformed anti-xenogeneic antibodies in the host mammal. Xenogeneic transplantation can be sub-divided into two categories, concordant and discordant, depending on the degree of genetic disparity between the donor and host species. Whereas transplantation between a rat and a mouse is considered concordant, transplantation between a mouse and a human, or a pig and a human is considered discordant. The host immune response to a discordant graft is significantly stronger than that observed to a concordant graft due primarily to the

increased frequency of natural preformed antibodies in the host that recognize discordant antigens and cause hyperacute rejection of the foreign tissue. Naturally occurring xenoantibodies can mediate hyperacute rejection (HAR) of xenogeneic tissue in as little as 2 hours (Kaufman et al., (1995), Annu. Rev. Immunol., Vol. 13, 339-367). Prevention of rejection in xenotransplants requires inhibition or suppression of multiple components of both the immune and inflammatory responses. According to Kaufman et al., " In experimental and clinical protocols in which immunosuppressive agents ... were administered to recipients of xenografts, vigorous rejection occurred , even when profoundly immunosuppressive combinations of agents were utilized, " (Kaufman et al. (1995), *supra*, page 347). The specification does not identify an immunosuppressive agent or combination of agents capable of rendering a recipient animal tolerant to xenogeneic or allogeneic tissue or provide sufficient guidance as to the level of immunodeficiency necessary to allow xenogeneic or allogenic cells to express therapeutic levels of any gene for a period of time sufficient to achieve any therapeutic effect on any disease or condition. The applicant working examples demonstrate β-galactosidase expression by syngeneic endothelial cells in an inbred strain of pigs. The applicant does not provide any evidence that xenogeneic or allogeneic cells can be transplanted into an immunocompetent host and elude host immune responses for a period of time sufficient to treat any disease or condition. Therefore, based on the art recognized potency of preformed anti-xenogeneic antibodies and other immune responses raised against foreign tissue, the lack of guidance as to methods of preventing anti-xenogeneic and anti-allogeneic host immune response, the lack of working examples

demonstrating xenogeneic or allogeneic transplantation, and the breadth of the claims, it would have required undue experimentation to practice the scope of the instant invention as claimed.

The specification fails to provide an enabling disclosure for the treatment of any condition by the site-specific installation of any type of syngeneic cells, transfected or untransfected, in any mammal. The specification is primarily directed to the administration of transfected endothelial cells to blood vessels *in vivo* for the treatment of cardiovascular conditions. The specification does not provide guidance for the administration of non-transformed cells or teach types of non-transformed cells which naturally secrete therapeutic levels of a protein such that the administration of the non-transfected cells results in the treatment of any disease or condition. The specification's working examples demonstrate the transfection of endothelial cells with a vector encoding lac-Z, and the installation of these cells by balloon catheter to blood vessels *in vivo*. The specification reports that the endothelial cells expressed detectable levels of β-galactosidase following transplantation. The specification also states that expression could be detected for approximately six weeks. However, the specification does not correlate the level of β-galactosidase with any therapeutic effect on any disease symptom or teach that the expression of similar levels of any other protein, such as FGF or tPA, for similar periods of time would result in any effect on any cardiovascular condition such as atherosclerosis, restenosis, or heart disease. The specification also fails to provide evidence that the delivery on any other type of transfected cell to any other cellular location using any method of delivery would result in the expression of therapeutic levels of protein or the treatment of any disease or condition. At the time of filing, the

therapeutic expression of genes using expression vectors and *ex vivo* methods was considered unpredictable. At the time of filing, Fred Ledley stated that, " [s]imple genetic defects are commonly corrected in cultured cells using gene transfer technologies. Few diseases, however, appear to be amenable to "cure" by somatic gene therapy at the present time. The disparity between *in vitro* and clinical opportunity reflects limitations in both basic and clinical technologies" (Ledley, (1991) Human Gene Therapy, Vol. 2, page 78, column 1-2, paragraph 6/1). Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2). In particular, Verma et al. cites an example of an *ex vivo* gene therapy attempt where a retrovirus was used to express factor IX in fibroblasts which were then grafted into an immunocompromised murine host. According to Verma, " within five to seven days of transplanting the infected cells back into mice, expression of factor IX is shut off ", and that appropriate enhancer-promoter combinations are necessary to override the 'off switch'. Verma concludes by stating that, "the search for such combinations is a case of trail and error for a given cell type" (Verma, (1997) Nature, 389, page 240). Orkin et al. concurs, stating that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene

therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4). Thus, in view of the art recognized unpredictability of achieving therapeutic levels of gene expression *in vivo* using transfected cells at the time of filing, the lack of guidance concerning the level and duration of gene expression of any gene from any transfected cell at any cellular location *in vivo* which correlates with any therapeutic effect on any disease or condition, the absence of working examples which demonstrate the expression of therapeutic levels of gene expression *in vivo* by transfected cells, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 120 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the method of claim 116, wherein the protein has a "diagnostic effect". It is unclear what the metes and bounds are of a protein which has a "diagnostic effect". It is unclear whether the protein can be used to identify the transfected cells in a diagnostic assay, or whether the expression of the protein itself would be "diagnostic" for some condition or disease. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 106, 109-111, 113-121, 123-124 and 131-134 are rejected under 35 U.S.C. 102(e) as being U.S. Patent No. 5,762,926 (7/22/97), hereafter referred to as Gage et al., which has an effective filing date of 12/15/1988. The applicant claims methods of introducing a protein or factor in a mammal by delivering to a blood vessel a transfected vascular cell comprising an exogenous nucleic acid encoding a factor or protein, and methods of treating a patient by site-specific installation of fibroblasts. The applicant further claims said methods wherein the cells are fibroblasts transfected *ex vivo* with a nucleic acid encoding a therapeutic gene, specifically a gene which encodes a protein competent to induce angiogenesis and revascularization, and wherein the cells are instilled intravenously to the brain, or are instilled surgically or percutaneously, or by injection.

Gage et al. teaches methods for treating defective or damaged cells in the CNS by grafting donor cells in the central nervous system which has been modified *ex vivo* to comprise a transgene which expresses a therapeutic amount of basic fibroblast growth factor (Gage et al., column 73,

claim 1). Gage et al. further teaches said method wherein the donor cells are fibroblasts and wherein the cells are introduced into the CNS by intravenous injection (Gage et al., columns 73 and 75, claims 2, 4, and 49-51). Gage et al. further teaches that the transfected fibroblasts or other types of cells can be implanted surgically into the brain or CNS or can be injected at various sites (Gage et al., column 20). Gage et al. also teaches that basic fibroblast growth factor is an angiogenic substance and that the production of bFGF by fibroblasts may promote angiogenesis and neovascularization (Gage et al., column 40, lines 14-23). Thus, by teaching all the elements of the claims as written, Gage et al. anticipates the instant invention.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER